Martindale

The complete drug reference

Thirty-second edition

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Multi-ingredient: *Fr.:* Arkotonic; *Ital.:* Biocarnil; Carpantin; Cerebrix†; Co-Carnetina B12; Normo-Calcium†; *Spain:* Hepadif; Histiotone†; Malandil; *UK:* Slimswift Day Trim†.

Choline Chloride (7875-g)

Choline Chloride *(rINN).*

Cholinii Chloridum. 2-Hydroxyethyltrimethylammonium chloride.

$C_5H_{14}ClNO$ = 139.6.

CAS — 62-49-7 (choline); 67-48-1 (choline chloride).

Pharmacopoeias. In *Aust.* and *Fr.*

Choline is an acetylcholine precursor. It is involved in lipid metabolism and acts as a methyl donor in various other metabolic processes. Choline has traditionally been considered to be a vitamin B substance although its functions do not justify its classification as a vitamin. Choline can be synthesised in the body. However, its absence in total parenteral nutrition causes hepatic steatosis, and it is also thought to be a requirement in the diet of neonates. Sources of choline, which occurs mostly as lecithin, include egg-yolk and vegetable and animal fat.

Choline is used as a dietary supplement and has been used to treat liver disorders such as fatty liver and cirrhosis. It has been tried in the management of Alzheimer's disease (p.1386) but without success. Choline is used as the bitartrate, dihydrogen citrate, and orotate salts as well as the chloride.

Human requirements. In the USA, an adequate intake of 550 mg daily in men and 425 mg daily in women has been determined for choline.[1]

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academy Press, 1998.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Becholine D†; *Fr.:* Hepagrume; *Ger.:* Neurotropan.

Multi-ingredient: *Aust.:* Orocholin; *Austral.:* Gingo A; Ginkgo ACE†; Liv-Detox; *Belg.:* Sulfarlem Choline; *Fr.:* Citrocholine; Citrocholine vit. C 250†; Cystichol; Desintex-Choline; Hepacholine Sorbitol; Kalicitrine; Liporex†; Phosphocholine†; Romarinex-Choline; *Ger.:* Enterotropin†; Hepabionta compt; Hepalipon N; Hepalixier†; Hepatofalk; Hepatofalk Neu; Hepavis†; Hepsan†; Neurotropan-Hy†; Neurotropan-M†; Orotofalk†; Sterofundin CH compositum†; Tutofusin LC†; *Ital.:* Citrosorbina B6†; Emofol†; Epa-Treis; Glutestere B-Complesso†; Itahepar†; Litrison; *S.Afr.:* Hepavite; *Spain:* Antibiofilus; Hepato Fardi; *Switz.:* Sebo Lotion†; *UK:* Fat-Solv; Lipotropic Factors; *USA:* Ak-Biocholine; Ilopan-Choline.

Chondroitin Sulphate–Iron Complex (14169-a)

Ferropolichondrum.

CAS — 54391-57-0.

Chondroitin sulphate-iron complex is employed as a source of iron (p.1346) for iron-deficiency anaemia (p.702). It is given by mouth in doses containing the equivalent of up to 90 mg of iron daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Condrofer; Ferrol; Isairon; *Jpn:* Blutal.

Chromium (18958-w)

Cr = 51.9961.

Chromium Trichloride (12560-s)

Chromic Chloride.

$CrCl_3$ = 158.4.

CAS — 10025-73-7 (anhydrous chromium trichloride); 10060-12-5 (chromium trichloride hexahydrate).

Pharmacopoeias. *US* has a monograph for chromium trichloride hexahydrate.

Chromium Trichloride Hexahydrate (USP 23) occurs as dark green, odourless, slightly deliquescent crystals. **Soluble** in water and in alcohol; slightly soluble in acetone; practically insoluble in ether. **Store** in airtight containers.

Adverse Effects

Trivalent salts of chromium, such as chromium trichloride, are generally considered to produce few adverse effects. However, hexavalent forms of chromium are notably toxic (see under Chromium Trioxide, p.1562).

Effects on the kidneys. Two cases of renal failure were attributed to ingestion of excessive doses of chromium picolinate (a trivalent chromium salt) in women with no previous history of renal dysfunction.[1,2] For mention of decreases in glomerular filtration rate in children receiving chromium-supplemented total parenteral nutrition, see below.

1. Wasser WG, *et al.* Chronic renal failure after ingestion of over-the-counter chromium picolinate. *Ann Intern Med* 1997; **126:** 410.
2. Cerulli J, *et al.* Chromium picolinate toxicity. *Ann Pharmacother* 1998; **32:** 428–31.

Uses and Administration

Chromium is an essential trace element that potentiates insulin action thus influencing carbohydrate, lipid, and protein metabolism. Dietary sources rich in chromium include brewers' yeast, meat, whole grains, and nuts. Chromium trichloride has been given as a chromium supplement in total parenteral nutrition. Chromium picolinate is used as a chromium supplement, and is being investigated for improving glycaemic control in patients with diabetes mellitus.

Human requirements. In the United Kingdom neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) (see p.1332) has been set for chromium although a safe and adequate intake was believed to be above 25 μg daily for adults.[1] Similarly, in the United States a recommended dietary allowance has not been published and the safe and adequate intake for adults was believed to be 50 to 200 μg daily.[2] WHO considers that the minimum population mean intake likely to meet normal needs for chromium might be approximately 33 μg daily, and that supplementation of this element should not exceed 250 μg daily until more is known.[3]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Subcommittee on the tenth edition of the RDAs, food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances.* 10th ed. Washington, DC: National Academy Press, 1989.
3. WHO. Chromium. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996: 155–60.

Supplementation. Although a daily chromium intake of 0.2 μg per kg body-weight has been suggested in children receiving total parenteral nutrition (TPN), a study in 15 children[1] receiving long-term parenteral nutrition found that supplementation at about this level was associated with serum-chromium concentrations 4 to 42 times higher than the mean value in 15 children not receiving TPN. Raised serum-chromium concentrations were associated with a decrease in glomerular filtration rate; one year after discontinuing chromium supplementation, which reduced intake to 0.05 μg per kg daily (as contaminants of water and TPN solutions), chromium concentrations, although lower, were still higher than controls and renal function had not altered. The authors have subsequently discontinued chromium supplementation in both children and adults, since chromium contamination of TPN solutions appears adequate to prevent deficiency, although it is acknowledged that signs of chromium deficiency may take some years to appear. Chromium contamination in various preparations used in paediatric parenteral nutrition has been studied.[2]

1. Moukarzel AA, *et al.* Excessive chromium intake in children receiving total parenteral nutrition. *Lancet* 1992; **339:** 385–8.
2. Hak EB, *et al.* Chromium and zinc contamination of parenteral nutrient solution components commonly used in infants and children. *Am J Health-Syst Pharm* 1998; **55:** 150–4.

Preparations

USP 23: Chromic Chloride Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Chrometrace†; *Canad.:* Micro Cr; *USA:* Chroma-Pak.

Multi-ingredient: *Austral.:* Digestaid; *Canad.:* Formula CI; *Fr.:* Bio-Chrome.

Citrulline (16582-n)

N^5-(Aminocarbonyl)-L-ornithine; N^5-Carbamylornithine.

α-Amino-δ-ureidovaleric acid.

$C_6H_{13}N_3O_3$ = 175.2.

CAS — 372-75-8.

Citrulline is an amino acid which is involved in the urea cycle. Citrulline and citrulline malate are used as dietary supplements.

Citrulline has been given as an alternative to arginine in the management of hyperammonaemia due to urea cycle disorders (p.1334).

Lysinuric protein intolerance is another condition associated with hyperammonaemia and similar neurological sequelae. In this condition there is no deficiency of urea-cycle enzymes but a deficiency of urea-cycle substrate, such as ornithine, which results in reduced synthesis of citrulline. Supplements of citrulline given with meals have been reported to have resulted in a substantial increase in protein tolerance, striking acceleration in linear growth, and an increase in bone mass in a child with this disorder who presented with osteoporosis.[1]

1. Carpenter TO, *et al.* Lysinuric protein intolerance presenting as childhood osteoporosis: clinical and skeletal response to citrulline therapy. *N Engl J Med* 1985; **312:** 290–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Stimol; *Switz.:* Stimufor†.

Multi-ingredient: *Fr.:* Epuram; *Ital.:* Citruplexina†; Energon Rende†; Ideolider; Ipoazotal; Ipoazotal Complex; Polilevo.

Cod-liver Oil (7890-v)

Cod-liver Oil *(BAN).*

Aceite de Hígado de Bacalao; Cod Liver Oil; Huile de Foie de Morue; Iecoris Aselli Oleum; Lebertran; Ol. Morrh.; Óleo de Bacalhau; Oleum Jecoris Aselli; Oleum Morrhuae; Olio di Fegato di Merluzzo.

CAS — 8001-69-2.

Pharmacopoeias. In *Eur.* (see p.viii), *Jpn, Pol.,* and *US.*

The fatty oil obtained from the fresh liver of the cod, *Gadus morrhua* and other species of Gadidae, solid substances being removed by cooling and filtering. Ph. Eur. includes Cod-liver Oil (Type A) and Cod-liver Oil (Type B). For both types, Ph. Eur. specifies not less than 600 units (180 μg) and not more than 2500 units (750 μg) of vitamin A per g and not less than 60 units (1.5 μg) and not more than 250 units (6.25 μg) of vitamin D (cholecalciferol) per g. The USP specifies not less than 850 units (225 μg) of vitamin A and not less than 85 units (2.125 μg) of vitamin D per g, and permits up to 1% of a suitable flavour or flavours.

A clear yellowish viscous liquid with a slightly fishy but not rancid odour. Practically **insoluble** in water; slightly soluble in alcohol; freely soluble in ether, in chloroform, in carbon disulphide, and in ethyl acetate; miscible with petroleum spirit. **Store** in well-filled airtight containers preferably under an inert gas. Protect from light.

Uses and Administration

Cod-liver oil is a rich source of vitamin D (p.1366) and a good source of vitamin A (p.1358). It also contains several essential fatty acids.

Cod-liver oil dressings or ointment have been advocated to accelerate healing in burns, ulcers, pressure sores, and superficial wounds, but controlled observations have failed to substantiate claims of their value.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Adecaps; *Austral.:* Hypol; *Belg.:* Surmoruine; *Ger.:* Unguentolan; *Ital.:* Dermovitamina; Merluzzina†; *Spain:* Aceite Geve Concentrado; *Switz.:* Morrhulan.

Multi-ingredient: *Aust.:* Dermilon†; Dermowund; Desitin; Leukichtan; Mirfulan; Pudan-Lebertran-Zinksalbe; Vitapan; Vulpuran; *Austral.:* Covitol†; Hypol; Mac†; Rashaway†; *Belg.:* Mitosyl; Newderm; Peneytol†; Polyseptol; Pyal; Vitamorrhuine; *Canad.:* Caldesene; Desitin; *Fr.:* Eryteal; Fletagex†; Halivite; *Ger.:* Adebilan†; Chlortesin-N†; Dermilon; Desitin; Elbozon†; Gelovitall†; Jacosulfon†; Kremulsion†; Leukona-Wundsalbe; Mirfulan; Mirfulan Spray N; Mitosyl; Rectosellan N†; Swansol-Wundsalbe†; *Irl.:* Caldease; Morhulin; *Ital.:* Dermosteril†; Fosfarsile Yunior; Idustatin; Neo-Ustiol; Steril Zeta; Trofo 5; Viocidina; *Norw.:* Aselli; Jecoderm†; *S.Afr.:* Achromide; Daromide†; Ung Vernleigh; *Spain:* Avril; Recto Menaderm; Siete Mares Higado Bacal; *Switz.:* Keroderm; Mitosyl†; Perles d'huile de foie de morue du Dr Geistlich; Phlogidermil; Vita-Hexin; Vita-Merfen†; *UK:* Hofels Cod Liver Oil and Garlic†; M & M; Morhulin; Scott's Emulsion; Woodwards Nappy Rash Ointment; *USA:* A and D Medicated; Caldesene; Clocream; Desitin; Diaparene Peri-Anal†; Diaper Rash; Dyprotex; Medicone Dressing; Primaderm-B.

Copper (5284-y)

Cu = 63.546.

CAS — 7440-50-8.

Calcium Copperedetate (12505-h)

Calcium [ethylenediaminetetra-acetato{4—}-*N,N',O,O'*]copper (II) dihydrate.

$C_{10}H_{12}CaCuN_2O_8.2H_2O$ = 427.9.

CAS — 66317-91-7 (anhydrous calcium copperedetate).

Pharmacopoeias. In *BP(Vet).*

A blue, odourless or almost odourless, crystalline powder. It contains 9.1 to 9.7% of Ca and 14.4 to 15.3% of Cu. Freely **soluble** in water, the solution gradually precipitating the insoluble tetrahydrate; practically insoluble in alcohol.

Copper Chloride (5288-k)

Cupric Chloride.

$CuCl_2.2H_2O$ = 170.5.

CAS — 7447-39-4 (anhydrous copper chloride); 10125-13-0 (copper chloride dihydrate).

Pharmacopoeias. In *US.*

Bluish-green deliquescent crystals. Freely **soluble** in water; soluble in alcohol; slightly soluble in ether. **Store** in airtight containers.

Copper Gluconate (18507-g)

Copper D-gluconate (1:2); Bis(D-gluconato-O^1,O^2) copper.
$C_{12}H_{22}CuO_{14}$ = 453.8.
CAS — 527-09-3.
Pharmacopoeias. In *US.*

Copper Sulphate (5285-j)

Copper Sulph.; Cuivre (Sulfate de); Cupr. Sulph.; Cupri Sulfas; Cupri Sulphas; Cupric Sulfate; Kupfersulfat; Sulfato de Cobre.
Copper (II) sulphate pentahydrate.
$CuSO_4.5H_2O$ = 249.7.
CAS — 7758-98-7 (anhydrous copper sulphate); 7758-99-8 (copper sulphate pentahydrate).

NOTE. Crude copper sulphate is sometimes known as 'blue copperas', 'blue stone', and 'blue vitriol'.

Pharmacopoeias. In *Eur.* (see p.viii) and *US. Eur.* also includes Anhydrous Copper Sulphate.

Blue crystals or crystalline powder. It slowly effloresces in air. The exsiccated salt is nearly white.

Soluble 1 in 3 of water, 1 in 0.5 of boiling water, 1 in 500 of alcohol, and 1 in 3 of glycerol; soluble in methyl alcohol. **Store** in airtight containers.

Anhydrous Copper Sulphate (Ph. Eur.) is a greenish grey, very hygroscopic, powder. Freely **soluble** in water; slightly soluble in methyl alcohol; practically insoluble in alcohol. **Store** in airtight containers.

Adverse Effects

Adverse effects from copper have tended to arise following absorption of the metal from cooking utensils and during dialysis. Ingestion of copper from cooking utensils is associated mainly with hepatotoxicity. Dialysis procedures may supply copper through the water supply or from parts of the equipment and when this happens patients may suffer haemolysis and other haematological reactions with kidney involvement as well as hepatotoxicity; the toxicity is generally a result of poor equipment maintenance.

Adverse effects attributed to copper have been reported in women with copper-containing intra-uterine devices. There have been isolated case reports of various effects such as allergy and endometrial changes. However, with these devices it is difficult to separate those adverse effects that are due to the device from those due solely to the copper.

The symptoms of Wilson's disease (hepatolenticular degeneration) (see p.992) are due to an accumulation of copper in various parts of the body.

Copper salts if ingested can produce severe gastro-intestinal effects and there may be systemic absorption of copper leading to the effects discussed above. The use of sprays of copper salts in agriculture has been associated with lung changes. Treatment of copper poisoning is symptomatic and may involve the use of a chelating agent to remove any absorbed metal. Dialysis has been tried.

Effects on the liver. A report of cirrhosis and acute liver failure attributable to chronic excessive copper supplement ingestion.[1]

1. O'Donohue J, *et al.* Micronodular cirrhosis and acute liver failure due to chronic copper self-intoxication. *Eur J Gastroenterol Hepatol* 1993; **5:** 561–2.

Interactions

Large doses of zinc supplements may inhibit the gastro-intestinal absorption of copper.

Uses and Administration

Copper is an essential trace element although severe copper deficiency, which is associated with anaemia, neutropenia, and bone demineralisation, is rare in humans. Copper sulphate is added to parenteral feeds as a source of copper in the prophylaxis and treatment of deficiency states. Doses that have been employed for prophylaxis range from 0.5 to 1.5 mg (7.9 to 23.6 μmol) of copper daily although up to 3 mg daily has been suggested in established deficiency; infants have received 20 μg (0.3 μmol) of copper per kg body-weight daily. The dose should be governed by the serum-copper concentration which in healthy adults ranges between 0.7 and 1.6 μg per mL (0.01 to 0.025 μmol per mL).

Copper sulphate and other soluble salts of copper have an astringent action on mucous surfaces and in strong solutions they are corrosive.

Copper has a contraceptive effect when present in the uterus and is added to some intra-uterine contraceptive devices; for further details, see below. It is also reported to have an antimicrobial action.

Copper sulphate has been used to prevent the growth of algae in reservoirs, ponds, and swimming pools and as a molluscicide in the control of fresh-water snails that act as intermediate hosts in the life-cycle of the parasites causing schistosomiasis.

Reagents containing copper sulphate are used in tests for reducing sugars.

In veterinary medicine calcium copperedetate, copper methionate, and cuproxoline are used for the prevention and treatment of copper deficiency.

Copper bracelets are worn as a folk remedy for rheumatic disorders: there is no good evidence to justify such a practice.

Copper (Cuprum Metallicum; Cuprum Met.) is used in homoeopathic medicine.

Contraception. In a statement from the Medical Advisory Committee of the Family Planning Association and the National Association of Family Planning Doctors in Great Britain the following points were made.[1] Intra-uterine devices (IUDs) are believed to exert their contraceptive effect (p.1434) by interfering with the reproductive process before the ovum reaches the intra-uterine cavity and the copper released from copper-bearing IUDs probably potentiates this effect. Like all devices which are placed in the uterus, copper IUDs are subject to deposition of cellular debris and of calcium and magnesium salts. The calcium and magnesium salts were once thought to reduce the effectiveness of IUDs, but this is not so as the copper ions are still able to diffuse. Copper IUDs first became available in the 1970s and in the early models the thin copper wire wound around the stem of the device sometimes fragmented or disappeared completely. Subsequent development led to devices that are both more effective and have a longer life. This has been achieved by increasing the wire thickness, by the preparation of a silver-core copper wire, and by the use of solid copper collars or sleeves on the device. The modern copper IUDs in use today should be regarded as being clinically effective and safe for at least five years. Copper IUDs are the most effective available method for postcoital contraception (p.1434). Traditional copper IUDs are T-shaped and rigid or semi-rigid. Newer forms include an implantable frameless device, which may be more suitable for nulliparous women.

1. Newton J, Tacchi D. Long-term use of copper intrauterine devices. *Lancet* 1990; **335:** 1322–3.

Deficiency states. Acquired copper deficiency is very rare and the small number of cases have usually involved patients on total parenteral nutrition or in one case[1] enteral nutrition.

In the United Kingdom dietary reference values (see p.1332) have been published for copper.[2] Although an estimated average requirement (EAR) could not be derived a reference nutrient intake (RNI) of 1.2 mg (19 μmol) daily was set for adults; RNIs of lower values were also specified for infants and children.[2]

In the United States a recommended dietary allowance has not been set for copper because of the uncertainty concerning the quantitative human requirements. Rather, a safe and adequate range has been specified of 1.5 to 3 mg daily for adults; lower values were also given for infants and children of various age groups.[3]

WHO has estimated a minimum population mean intake of 1.2 mg daily for women and 1.3 mg daily for men, and safe upper limits of population mean intakes of 10 mg daily for women and 12 mg daily for men;[4] values are also estimated for infants and children.

Menkes' disease is an X-linked genetic disorder associated with a defect in copper transport, which almost invariably results in death due to progressive cerebral degeneration by the age of 3 years. Early initiation of treatment with copper-histidine complex may be of benefit in such children.[5]

1. Masugi J, *et al.* Copper deficiency anemia and prolonged enteral feeding. *Ann Intern Med* 1994; **121:** 386.
2. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
3. Subcommittee on the tenth edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances.* 10th ed. Washington, DC: National Academy Press, 1989.
4. WHO. Copper. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996: 123–43.
5. Sarkar B, *et al.* Copper-histidine therapy for Menkes' disease. *J Pediatr* 1993; **123:** 828–30.

Schistosomiasis. Although most control programmes for schistosomiasis (p.95) use niclosamide as a molluscicide, and copper salts have largely been abandoned for snail control, copper sulphate is still used for this purpose in Egypt.[1]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993.

Preparations

BPC 1973: Compound Ferrous Sulphate Tablets;
USP 23: Cupric Chloride Injection; Cupric Sulfate Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Coppertrace†; Multiload; ***Canad.:*** Gyne-T; Micro Cu; *Fr.:* Gyne-T; Metacuprol; ML Cu 250; ML Cu 375; Remoplexe; Sterilet T au Cuivre†; ***Ger.:*** Cuprenase†; Gyne-T; Multiload; ***Ital.:*** Multiload; Ortho Gyne-T; ***Ital.:*** Copper T†; Gravigard; Mini-Gravigard; ML Cu 250†; No-Gravid; Ortho-Neo-T†; Telo Cypro; ***Neth.:*** Gyne-T; Multiload; ***S.Afr.:*** Cuprocept CCL; Dalcept; Fincoid†; Multiload; Tricept; ***Switz.:*** Fincoid; Multiload; SOF-T; ***UK:*** Gynefix; Multiload; Novagard†; Ortho Gyne-T; ***USA:*** Cu-7†; Paragard T380A; Tatum-T†.

Multi-ingredient: ***Austral.:*** Alcusal; Alcusal Sport; Ascoxal; ***Canad.:*** Nova-T; ***Fr.:*** Bioceanat; Dermalibour; Dermo-Sulfuryl; Dermocreme; Dermocuivre; Dexaderme Kefranet†; Femiplexe; Laccoderme Dalibour†; Nova-T; Oligoderm; Ramet Dalibour; Ramet Pain; Sanoformine; Septalibour; Tot'hema; Vitacuivre†; ***Ger.:*** Nova-T; Silvapin Sauerstoffbad mit Fichtennadelol†; Silvapin Sauerstoffbad†; Sulfolitruw†; ***Irl.:*** Ferrotab; ***Ital.:*** Nova-T; Silver-Nova T†; ***Neth.:*** Nova-T; ***Norw.:*** Ascoxal; ***S.Afr.:*** Nova-T; ***Spain:*** Acnosan; Ferroce†; ***Swed.:*** Ascoxal; ***Switz.:*** Nova-T; ***UK:*** Folicin†; Foresight Iron Formula; Nova-T; ***USA:*** ORA5.

Cyclamic Acid (2389-r)

Cyclamic Acid *(BAN, USAN).*

Cyclam. Acid; E952; Hexamic Acid. *N*-Cyclohexylsulphamic acid.

$C_6H_{13}NO_3S$ = 179.2.
CAS — 100-88-9.

Calcium Cyclamate (2379-t)

Calc. Cyclam.; Calcium Cyclohexanesulfamate; Cyclamate Calcium; E952. Calcium *N*-cyclohexylsulphamate dihydrate.

$C_{12}H_{24}CaN_2O_6S_2.2H_2O$ = 432.6.
CAS — 139-06-0 (anhydrous calcium cyclamate); 5897-16-5 (calcium cyclamate dihydrate).

Sodium Cyclamate (2409-s)

Sodium Cyclamate *(BAN, rINN).*

Cyclamate Sodium; E952; Natrii cyclamas; Sod. Cyclam.; Sodium Cyclohexanesulphamate. Sodium *N*-cyclohexylsulphamate.

$C_6H_{12}NNaO_3S$ = 201.2.
CAS — 139-05-9.

Pharmacopoeias. In *Eur.* (see p.viii).

White crystalline powder or colourless crystals. Freely **soluble** in water; slightly soluble in alcohol; very slightly soluble in ether. A 10% solution in water has a pH of 5.5 to 7.5.

Cyclamic acid and its calcium and sodium salts are intense sweetening agents. In dilute solutions (up to about 0.17%) sodium cyclamate is about 30 times as sweet as sucrose but this factor decreases at higher concentrations. When the concentration approaches 0.5%, a bitter taste becomes noticeable. It is stable to heat.

The use of cyclamates as artificial sweeteners in food, soft drinks, and artificial sweetening tablets was at one time prohibited in Great Britain and some other countries because of concern about the metabolite cyclohexylamine, but has since been reappraised to allow their use.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Sucaryl.

Multi-ingredient: ***Austral.:*** Sucaryl; ***Fr.:*** Humex†; Sucaryl; ***Ital.:*** Diet Sucaryl.

Cysteine (16183-s)

Cysteine *(rINN).*

C; Cys; L-Cysteine. L-2-Amino-3-mercaptopropionic acid.

$C_3H_7NO_2S$ = 121.2.
CAS — 52-90-4.

Pharmacopoeias. In *Ger.*

Cysteine Hydrochloride (579-e)

Cysteine Hydrochloride *(rINNM).*

920; Cys Hydrochloride; L-Cysteine Hydrochloride Monohydrate; Cysteini Hydrochloridum Monohydricum. L-2-Amino-3-mercaptopropionic acid hydrochloride monohydrate.

$C_3H_7NO_2S.HCl.H_2O$ = 175.6.
CAS — 52-89-1 (anhydrous L-cysteine hydrochloride); 7048-04-6 (L-cysteine hydrochloride monohydrate).

Pharmacopoeias. In *Eur.* (see p.viii) and *US.*

White or colourless crystals or crystalline powder. Ph. Eur. **solubilities** are: freely soluble in water; slightly soluble in alcohol; practically insoluble in ether. USP solubilities are: soluble in water, in alcohol, and in acetone.

Cysteine is an aliphatic amino acid. Cysteine and cysteine hydrochloride are used as dietary supplements.

Cysteine and cysteine hydrochloride are included in preparations used in ophthalmology; eye drops have been used to prevent corneal ulceration after chemical burns.

Cysteine, like other sulfhydryl-containing drugs, could produce a false-positive result in the nitroprusside test for ketone bodies used in diabetes and suspected hepatocellular injury.[1]

1. Csako G, Elin RJ. Unrecognized false-positive ketones from drugs containing free-sulfhydryl group(s). *JAMA* 1993; **269:** 1634.

Preparations

USP 23: Cysteine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Ginkgo ACE†; ***Fr.:*** Co-A†; Lobamine-Cysteine; Phakan; Vita-Iodurol; Vita-Iodurol ATP; ***Ger.:*** Cheihepar†; Choldestal†; Hepalixier†; Hepaticum "Mletz-

Leucine (597-y)

Leucine *(USAN, rINN)*.

α-Aminoisocaproic Acid; L; Leu; L-Leucine; Leucinum. L-2-Amino-4-methylvaleric acid.

$C_6H_{13}NO_2$ = 131.2.

CAS — 61-90-5.

Pharmacopoeias. In *Eur.* (see p.viii), *Jpn*, and *US*.

Shiny flakes or a white or almost white, practically odourless crystalline powder. Sparingly **soluble** in water; practically insoluble in alcohol and in ether. It dissolves in dilute solutions of mineral acids and of alkali hydroxides. A 1% solution in water has a pH of 5.5 to 7.0. **Protect** from light.

Leucine is a branched-chain amino acid which is an essential constituent of the diet. It is used as a dietary supplement. It is also an ingredient of several preparations that have been promoted for disorders of the liver.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Revitalose; ***Ger.:*** Bramin-hepa; Falkamin; Lactostrict†; ***Ital.:*** Falkamin; Isobranch; Isoram.

Lysine (12141-y)

Lysine *(USAN, rINN)*.

K; Lys; L-Lysine. L-2,6-Diaminohexanoic acid.

$C_6H_{14}N_2O_2$ = 146.2.

CAS — 56-87-1.

Pharmacopoeias. In *Ger.* as the monohydrate.

Lysine Acetate (669-y)

Lysine Acetate *(rINNM)*.

Lys Acetate; L-Lysine Monoacetate. L-2,6-Diaminohexanoic acid acetate.

$C_6H_{14}N_2O_2,C_2H_4O_2$ = 206.2.

CAS — 57282-49-2.

Pharmacopoeias. In *US*.

White odourless crystals or crystalline powder. Freely **soluble** in water.

Lysine Hydrochloride (599-z)

Lysine Hydrochloride *(USAN, rINNM)*.

Lys Hydrochloride; L-Lysine Monohydrochloride; Lysini Hydrochloridum. L-2,6-Diaminohexanoic acid hydrochloride.

$C_6H_{14}N_2O_2.HCl$ = 182.6.

CAS — 657-27-2.

Pharmacopoeias. In *Eur.* (see p.viii), *Jpn*, and *US*.

A white odourless crystalline powder or colourless crystals. Freely **soluble** in water; slightly soluble in alcohol; practically insoluble in ether. **Protect** from light.

Lysine is an aliphatic amino acid which is an essential constituent of the diet. Lysine and lysine hydrochloride are used as dietary supplements.

Hyperargininaemia. Lysine has been used with ornithine to manage symptoms in a patient with hyperargininaemia—see under Hyperammonaemia, p.1334.

Preparations

Proprietary Preparations (details are given in Part 3)

Switz.: Ambifon†; ***USA:*** Enisyl†.

Multi-ingredient: ***Austral.:*** Cold Sore Relief; Cold Sore Tablets; Incremin Iron; Vitaline; ***Canad.:*** Coba-12†; ***Fr.:*** Acti 5; Curasten; Revitalose; ***Ital.:*** Biocarnil; Calciofix; Cerebrix†; Combivit†; Gliviton†; Incremin; Oroticon Lisina†; ***Spain:*** Acticinco; Calcioretard; Euzymina Lisina; Malandil; ***UK:*** Amino MS; Labophylline†; ***USA:*** Klorvess.

Malt Extract (601-c)

Extractum Bynes.

It contains 50% or more of maltose, together with dextrin, glucose, and small amounts of other carbohydrates, and protein. It is prepared from malted grain of barley (*Hordeum distichon* or *H. vulgare*) or a mixture of this with not more than 33% of malted grain of wheat (*Triticum aestivum* or *T. turgidum*).

Malt extract has nutritive properties. It is chiefly used as a vehicle in preparations containing cod-liver oil (p.1337) and halibut-liver oil (p.1345). It is a useful flavouring agent for masking bitter tastes.

A product known as malt soup extract, obtained from barley grains, and containing 73% maltose together with 12% other polymeric carbohydrates as well as small amounts of proteins, electrolytes, and vitamins, is sometimes used as a laxative. For discussion of constipation and its management, see p.1168.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Maltsupex.

Multi-ingredient: ***Austral.:*** Waterbury's Compound†; ***Fr.:*** Elixir Contre La Toux Weleda; Galactogil; ***Ital.:*** Syllamalt†; ***Switz.:*** Optilax; ***USA:*** Syllamalt.

Maltitol (13690-b)

E965; Hydrogenated Maltose; D-Maltitol; Maltitolum. α-D-Glucopyranosyl-1,4-D-glucitol.

$C_{12}H_{24}O_{11}$ = 344.3.

CAS — 585-88-6.

Pharmacopoeias. In *Eur.* (see p.viii).

A white crystalline powder. Very **soluble** in water; practically insoluble in alcohol.

Maltitol Syrup (10169-s)

E965; Hydrogenated Glucose Syrup; Hydrogenated High Maltose-glucose Syrup; Liquid Maltitol; Maltitolum Liquidum.

Pharmacopoeias. In *Eur.* (see p.viii).

A clear, colourless, syrupy liquid. It is an aqueous solution of a hydrogenated, part hydrolysed starch, containing not less than 70% w/w of solid matter composed of a mixture of mainly maltitol with sorbitol and hydrogenated oligo- and polysaccharides. On the dried basis, it contains not less than 50% of maltitol and not more than 8% of sorbitol. **Miscible** with water and with glycerol.

Hydrogenated glucose syrup is a generic term encompassing products of widely varying composition and it was concluded that such products containing up to 90% of maltitol should more properly be called maltitol syrup.[1] This was subsequently amended to include products containing up to 98% maltitol.[2] Preparations containing a minimum of 98% of maltitol were designated the title maltitol.

1. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-third report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 776* 1989.
2. FAO/WHO. Evaluation of certain food additives and contaminants: forty-first report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 837* 1993.

Maltitol and maltitol syrup are bulk sweeteners used in foods; they are considered to be less cariogenic than sucrose. The ingestion of large quantities may produce flatulence and diarrhoea.

Preparations

USNF 18: Maltitol Solution.

Maltodextrin (602-k)

Pharmacopoeias. In *Swiss.* Also in *USNF*.

A glucose polymer prepared by the partial hydrolysis of starch.

White hygroscopic powder or granules. Freely **soluble** or readily dispersible in water; slightly soluble to practically insoluble in dehydrated alcohol. A 20% solution has a pH of between 4 and 7. **Store** in airtight containers at a temperature not exceeding 30° and a relative humidity not exceeding 50%.

Maltodextrin, a malto-oligosaccharide, is a source of carbohydrate often used in oral dietary supplements and tube feeding. Glucose is rapidly released in the gastro-intestinal tract but because of the high average molecular weight of maltodextrin, solutions have a lower osmolarity than isocaloric solutions of glucose. Additionally, preparations based on maltodextrin and intended for dietary supplementation usually have a low electrolyte content and are free of other sugars such as fructose, galactose, lactose, and sucrose. These properties make such preparations suitable for dietary supplementation in a variety of diseases including certain gastrointestinal disorders where malabsorption is a problem, in disaccharide intolerance (without isomaltose intolerance), and in acute and chronic hepatic and renal diseases where protein, mineral, and fluid restriction are often necessary.

Maltodextrin is also employed as a pharmaceutical excipient.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Maxijul; ***Canad.:*** Moducal†; ***Irl.:*** Fibrosine; ***Ital.:*** Fantomalt; Maltovis.

Multi-ingredient: ***Fr.:*** Gumilk; ***Ital.:*** Doldieta.

Maltose (603-a)

4-*O*-α-D-Glucopyranosyl-β-D-glucopyranose.

$C_{12}H_{22}O_{11}$ = 342.3.

CAS — 69-79-4 (anhydrous maltose); 6363-53-7 (maltose monohydrate).

Pharmacopoeias. In *Jpn*.

It is obtained from starch by hydrolysis with amylase. The hydration of maltose depends on the solvent from which it is crystallised.

Maltose, a disaccharide composed of two glucose molecules, is less sweet than sucrose. It is often present with other sugars in mixtures used as carbohydrate sources.

Adverse effects. Hyponatraemia developed in a patient with acute renal failure after liver transplantation following intravenous infusion of normal immunoglobulin in 10% maltose.[1] The effect which recurred on each of four successive infusions resembled that of hyperglycaemia and was thought to be due to accumulation of maltose and other osmotically active metabolites in the extracellular fluid.

1. Palevsky PM, *et al.* Maltose-induced hyponatremia. *Ann Intern Med* 1993; **118:** 526–8.

Preparations

USNF 18: Liquid Glucose.

Proprietary Preparations (details are given in Part 3)

Jpn: Martos-10.

Multi-ingredient: ***Fr.:*** Picot.

Manganese (5303-d)

Mn = 54.938049.

CAS — 7439-96-5.

Manganese Chloride (18463-w)

$MnCl_2.4H_2O$ = 197.9.

CAS — 7773-01-5 (anhydrous manganese chloride); 13446-34-9 (manganese chloride tetrahydrate).

Pharmacopoeias. In *US*.

Large, irregular, pink, odourless, translucent crystals. **Soluble** in water and alcohol; practically insoluble in ether. **Store** in airtight containers. A 5% solution has a pH between 3.5 and 6.0.

Manganese Gluconate (18506-v)

Bis(D-gluconato-O^1,O^2) manganese; Manganese D-gluconate.

$C_{12}H_{22}MnO_{14}$ = 445.2.

Pharmacopoeias. In *US* which allows either the anhydrous or dihydrate form.

Manganese Sulphate (5304-n)

Manganese Sulfate. Manganese (II) sulphate tetrahydrate.

$MnSO_4.4H_2O$ = 223.1.

CAS — 7785-87-7 (anhydrous manganese sulphate); 10034-96-5 (manganese sulphate monohydrate); 10101-68-5 (manganese sulphate tetrahydrate).

Pharmacopoeias. In *Br.* and *Fr. Br., Fr.*, and *US* include the monohydrate.

Manganese Sulphate (BP 1998) (the tetrahydrate form) is described as pale pink odourless or almost odourless crystals or crystalline powder. Freely **soluble** in water; practically insoluble in alcohol.

Manganese Sulphate Monohydrate (BP 1998) is described as pale red hygroscopic crystals. Freely **soluble** in water; practically insoluble in alcohol. **Store** in airtight containers.

Manganese Sulfate (USP 23) (the monohydrate form) is described as pale red, slightly efflorescent crystals, or purple, odourless powder. **Soluble** in water; insoluble in alcohol. **Store** in airtight containers.

Adverse Effects

Acute poisoning due to ingestion of manganese or manganese salts is rare. The main symptoms of chronic poisoning, either from injection or usually inhalation of manganese dust or fumes in air, include extrapyramidal symptoms that can lead to progressive deterioration in the central nervous system.

Cholestatic liver disease, and possibly changes in the basal ganglia, have been reported to be associated with hypermanganesaemia in children receiving long-term parenteral nutrition;[1,2] manganese accumulation may be secondary to impaired biliary excretion.[3] Manganese supplementation in such patients requires re-appraisal and whole blood manganese concentrations should be monitored regularly. A low-dose regimen of not more than 1 μg (0.018 μmol) per kg body-weight daily has been suggested,[2,3] which is the dose recommended by the American Society of Clinical Nutrition.[4] Manganese accumulation in the basal ganglia has been observed in patients with liver cirrhosis.[5]

1. Reynolds AP, *et al.* Manganese in long term paediatric parenteral nutrition. *Arch Dis Child* 1994; **71:** 527–8.
2. Fell JME, *et al.* Manganese toxicity in children receiving long-term parenteral nutrition. *Lancet* 1996; **347:** 1218–21.
3. Beath SV, *et al.* Manganese toxicity and parenteral nutrition. *Lancet* 1996; **347:** 1773–4. Correction. *ibid.* **348:** 416.
4. Greene HL, *et al.* Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of The American Society for Clinical Nutrition. *Am J Clin Nutr* 1988; **48:** 1324–42.

5. Krieger D, *et al.* Manganese and chronic hepatic encephalopathy. *Lancet* 1995; **346**: 270–4.

Pharmacokinetics

Absorption of manganese from the gastro-intestinal tract is variable, ranging from 3 to 50%. There is some evidence that the amount absorbed decreases as intake increases, suggesting a homoeostatic response. In the circulation, manganese is bound to transmanganin, a beta-1-globulin. Manganese is stored in the brain, kidneys, pancreas, and liver. It is excreted in bile, and undergoes enterohepatic circulation.

Uses and Administration

Manganese is an essential trace element and small amounts of a salt such as the chloride or sulphate are sometimes added to solutions for total parenteral nutrition. Suggested doses are 275 µg (5 µmol) elemental manganese daily for adults and children over 40 kg body-weight, and 1 µg (0.0182 µmol) per kg body-weight for infants and children to a maximum of 15 µg (see also under Adverse Effects, above).

Manganese compounds or salts that have been used in therapeutics in addition to those mentioned above include manganese amino acid chelate, manganese dioxide, manganese gluconate, and manganese hydrogen citrate.

Human requirements. In the United Kingdom neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) (see p.1332) has been set for manganese although a safe intake for adults was believed to lie above 1.4 mg (26 µmol) daily.[1] Similarly, in the United States a recommended dietary allowance has not been published but the safe and adequate range for adults was considered to be 2 to 5 mg daily.[2] WHO has not proposed a safe range of mean population intakes for manganese since neither intakes resulting in deficiency nor threshold toxicity levels have been established.[3] Diets high in unrefined cereals, nuts, leafy vegetables, and tea will be high in manganese.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Subcommittee on the tenth edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances*. 10th ed. Washington, DC: National Academy Press, 1989.
3. WHO. Manganese. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996; 163–7.

Preparations

BPC 1973: Compound Ferrous Sulphate Tablets;
USP 23: Manganese Chloride Injection; Manganese Sulfate Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Mangatrace†; *Canad.:* Micro Mn; *Fr.:* Mangaplexe.

Multi-ingredient: *Fr.:* Dienol†; Ionarthrol; Megasthenyl; Oligoderm; Tot'hema; *Ger.:* Aksekapseln†; diabetoSome (Revitorgan)†; Sulfolitruw†; *Irl.:* Ferrotab; *Ital.:* Ferrlecit†; *UK:* Folicin†.

Molybdenum (16901-d)

Mo = 95.94.

Ammonium Molybdate (18365-p)

Hexaammonium molybdate tetrahydrate.
$(NH_4)_6Mo_7O_{24}.4H_2O$ = 1235.9.
CAS — 12054-85-2.
Pharmacopoeias. In *US.*

Colourless or slightly green or yellow crystals. **Soluble** in water; practically insoluble in alcohol. **Store** in airtight containers.

Sodium Molybdate (18511-h)

Na_2MoO_4 = 205.9.
Pharmacopoeias. In *Ger.*, which also includes a monograph for the dihydrate.

Adverse Effects

Very high intakes of molybdenum, and associated increases in xanthine oxidase activity, may result in hyperuricaemia, and possibly gout. Molybdenum intoxication may impair the utilisation of copper.

Uses and Administration

Molybdenum is an essential trace element and small amounts, in the form of ammonium molybdate or sodium molybdate, are sometimes added to solutions for total parenteral nutrition. A suggested dose is about 20 to 120 µg (0.2 to 1.2 µmol) elemental molybdenum daily.

Ammonium molybdate is used in veterinary medicine to treat copper poisoning in sheep.

Human requirements. In the United Kingdom neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) (see p.1332) has been set for molybdenum although a safe intake was believed to be between 50 and 400 µg (0.5 and 4 µmol) daily for adults.[1] Similarly, in the United States a recommended dietary allowance has not been published but a safe and adequate range was considered to be 75 to 250 µg daily for adults.[2] WHO make the suggestion that the adult basal requirement for molybdenum could be about 25 µg daily, corresponding to approximately 0.4 µg per kg body-weight.[3]

Foods contributing to dietary molybdenum include milk, beans, breads, and cereals; however, extreme regional variations occur in molybdenum contents of food crops due to soil differences.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Subcommittee on the tenth edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances*. 10th ed. Washington, DC: National Academy Press, 1989.
3. WHO. Molybdenum. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996; 144–54.

Preparations

USP 23: Ammonium Molybdate Injection.

Proprietary Preparations (details are given in Part 3)
Fr.: Molybdene Injectable; *USA:* Molypen.

Multi-ingredient: *Ger.:* Sulfolitruw†.

Monosodium Glutamate (617-n)

621; Chinese Seasoning; MSG; Natrii Glutamas; Sodium Glutamate. Sodium hydrogen L-(+)-2-aminoglutarate monohydrate.
$C_5H_8NNaO_4.H_2O$ = 187.1.
CAS — 142-47-2 (anhydrous).
Pharmacopoeias. In *USNF. Chin.* includes the injection.

White, practically odourless, free-flowing crystals or crystalline powder. It may have either a slightly sweet or slightly salty taste. Monosodium glutamate 32 g is approximately equivalent to anhydrous monosodium glutamate 29 g or glutamic acid 25 g. Freely **soluble** in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 6.7 to 7.2. **Store** in airtight containers.

Monosodium glutamate is widely used as a flavour enhancer and imparts a meaty flavour.

In susceptible individuals, ingestion of foods containing monosodium glutamate may result in flushing, facial pressure, chest pain, headache, and nausea. The symptoms tend to occur within an hour of eating 3 g or more of monosodium glutamate on an empty stomach.

Nicotinic Acid (7865-b)

Nicotinic Acid *(rINN).*

375; Acidum Nicotinicum; Niacin; Nikotinsäure. Pyridine-3-carboxylic acid.
$C_6H_5NO_2$ = 123.1.
CAS — 59-67-6.

NOTE. Some published sources use the term niacin as a generic term to include both nicotinic acid and nicotinamide; in the USP the title niacin is applied specifically to nicotinic acid.
Pharmacopoeias. In *Chin., Eur.* (see p.viii), *Int., Jpn,* and *US.*

White, odourless or almost odourless, crystals or crystalline powder.

Soluble 1 in 60 of water; soluble or freely soluble in boiling water and in boiling alcohol; practically insoluble in ether; dissolves in dilute solutions of alkali hydroxides and carbonates. **Protect** from light.

Nicotinamide (7864-m)

Nicotinamide *(rINN).*

Niacinamide; Nicotinamidum; Nicotinic Acid Amide; Nicotylamide; Vitamin B_3; Vitamin PP. Pyridine-3-carboxamide.
$C_6H_6N_2O$ = 122.1.
CAS — 98-92-0.
Pharmacopoeias. In *Chin., Eur.* (see p.viii), *Int., Jpn, Pol.,* and *US.*

A white crystalline powder or colourless crystals, odourless or with a faint characteristic odour. **Soluble** 1 in 1.5 of water, 1 in 10 of boiling water, and 1 in 5.5 of alcohol; slightly soluble in ether; soluble in glycerol. A 5% solution in water has a pH of 6.0 to 7.5. **Store** in airtight containers.

Adverse Effects and Treatment

Nicotinic acid has a vasodilator action and when given by mouth or by injection in therapeutic doses it may cause flushing, a sensation of heat, faintness, and a pounding in the head. These symptoms are transient and various strategies have been proposed to reduce them (see below). Nicotinamide does not have a vasodilator action.

Other adverse effects which have been reported, especially following high doses of nicotinic acid, include dryness of the skin, pruritus, hyperpigmentation, abdominal cramps, diarrhoea, nausea and vomiting, anorexia, activation of peptic ulcer, amblyopia, jaundice and impairment of liver function, decrease in glucose tolerance, hyperglycaemia, and hyperuricaemia. Most of these effects subside on withdrawal of the drug.

Topical nicotinamide may cause dryness of the skin and, less frequently, pruritus, erythema, burning sensation, and irritation.

Nicotinic acid produces frequent adverse effects, but they are not usually serious, tend to decrease with time, and some can be minimised by following appropriate instructions for use.[1,2] Dermal and gastro-intestinal reactions are most common. Truncal and facial flushing are reported in 90 to 100% of treated patients in large clinical trials; they appear to be prostaglandin-mediated and can be reduced with aspirin 75 mg or 325 mg given shortly before nicotinic acid administration, or simply by giving the nicotinic acid with food, and by starting therapy with a low dose and gradually increasing this. Flushing may be less common with modified-release formulations.[2] Significant elevations of liver enzymes are occasionally seen with nicotinic acid therapy. They are more common in patients given large dosage increases over short periods of time, and in patients treated with modified-release formulations. Palumbo[3] has suggested that since effects on liver function may in some instances lead to hepatic failure and are more common with modified-release dosage forms the use of crystalline immediate-release preparations should be preferred, a view shared by other commentators.[4] However, although studies appear to confirm a more frequent association of hepatotoxicity with modified-release dosage forms[5-7] it should be borne in mind that these effects can also occur with the immediate-release preparations, especially at high doses. There is also a suggestion that not all modified-release preparations are alike in their effects.[8] (For further references to hepatotoxicity, see below.)

Nicotinic acid can reduce glucose tolerance, and this may be problematic in patients with diabetes mellitus,[2,4] although nicotinamide has been investigated in the prevention of diabetes mellitus (see below). Nicotinic acid also decreases urinary excretion of uric acid, which may result in elevation of serum uric acid and exacerbation of pre-existing gout.[2]

1. Knodel LC, Talbert RL. Adverse effects of hypolipidaemic drugs. *Med Toxicol* 1987; **2**: 10–32.
2. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54**: 2815–19.
3. Palumbo PJ. Rediscovery of crystalline niacin. *Mayo Clin Proc* 1991; **66**: 112–13.
4. Kreisberg RA. Niacin: a therapeutic dilemma—"one man's drink is another's poison". *Am J Med* 1994; **97**: 313–16.
5. McKenney JM, *et al.* A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; **271**: 672–7.
6. Rader JI, *et al.* Hepatic toxicity of unmodified and time-release preparations of niacin. *Am J Med* 1992; **92**: 77–81.
7. Gray DR, *et al.* Efficacy and safety of controlled-release niacin in dyslipoproteinemic veterans. *Ann Intern Med* 1994; **121**: 252–8.
8. Lavie CJ, Milani RV. Safety and side-effects of sustained-release niacin. *JAMA* 1994; **272**: 513–14.

Effects on the eyes. Retrospective survey of hyperlipidaemic patients suggested that dry eyes (sicca syndromes), blurred vision, and swollen eyelids might be associated with nicotinic acid therapy in some patients.[1] The effects appeared to be dose-related and reversible. In 2 patients treatment was discontinued because of symptoms suggestive of cystoid macular oedema. Three other cases of nicotinic acid maculopathy have been reported.[2]

1. Fraunfelder FW, *et al.* Adverse ocular effects associated with niacin therapy. *Br J Ophthalmol* 1995; **79**: 54–6.
2. Callanan D, *et al.* Macular edema associated with nicotinic acid (niacin). *JAMA* 1998; **279**: 1702.

Effects on the liver. As mentioned above hepatotoxicity may occur with nicotinic acid, particularly at high doses or with modified-release dosage forms, but toxicity at low doses and with immediate-release preparations has also been seen.

Further references.

1. Mullin GE, *et al.* Fulminant hepatic failure after ingestion of sustained-release nicotinic acid. *Ann Intern Med* 1989; **iii**: 253–5.
2. Knopp RH. Niacin and hepatic failure. *Ann Intern Med* 1989; **iii**: 769.
3. Henkin Y, *et al.* Rechallenge with crystalline niacin after drug-induced hepatitis from sustained-release niacin. *JAMA* 1990; **264**: 241–3.
4. Hodis HN. Acute hepatic failure associated with the use of low-dose sustained-release niacin. *JAMA* 1990; **264**: 181.
5. Etchason JA, *et al.* Niacin-induced hepatitis: a potential side effect with low-dose time-release niacin. *Mayo Clin Proc* 1991; **66**: 23–8.
6. Rader JI, *et al.* Hepatic toxicity of unmodified and time-release preparations of niacin. *Am J Med* 1992; **92**: 77–81.